HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY 07110 • TELEPHONE (201) 235-5000 • (N.Y.C.) 695-1400

RESEARCH DIVISION

April 29, 1980

Dr. Attallah Kappas
Professor and Physician-in-Chief
The Rockefeller University
New York, NY 10021

Dear Kapp,

The differential induction of epoxide hydrase relative to cytochrome P-450 can be either good or bad for the organism depending on the substrate studied. Although elevated levels of epoxide hydrase generally enhance the detoxification of arene oxides and epoxides, epoxide hydrase can also play a critical role in the metabolic activation of chemicals.

Epoxide hydrase metabolizes the strong mutagen, benzo(a)pyrene 4,5-oxide, to the nonmutagenic benzo(a)pyrene 4,5-dihydrodiol very readily. In this case, epoxide hydrase acts to detoxify an environmental chemical.

In contrast to the above detoxifying role of epoxide hydrase in the metabolism of a chemical, benzo(a)pyrene-7,8-oxide is a very weak mutagen that requires both cytochrome P-450 and epoxide hydrase for metabolic activation to the strongly mutagenic benzo(a)pyrene-7,8-diol-9,10-epoxides. The later diol-epoxides are very poor substrates for epoxide hydrase. Incidentally, our studies showing that epoxide hydrase is required for the metabolic activation of benzo(a)pyrene 7,8-oxide provided the first demonstration of a direct role of epoxide hydrase in the metabolic activation of a chemical to a toxic product. I have enclosed a couple of reprints that describe these studies.

With warm personal regards!

Sincerely yours,

Allan H. Conney, Ph.D.

AHC/ljg
Enclosures